● PRINTER RUSH ●
(PTO ASSISTANCE)

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[RUSH] **MESSAGE:** please provide missing serial numbers on pages 26, line 9 & page 34, line 11.

THANK YOU

[XRUSH] **RESPONSE:** Done

INITIALS: [illegible]

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REV 10/04

the substrate. Fluid flow in these fractally constructed flow systems is very sensitive to fluid viscosity and to the development of flow restriction caused, for example, by the proliferation of cells, or the agglomeration of cells, particles, or macromolecular complexes that may be present in a sample. The detection of the presence of an analyte based on flow restriction is described in USSN 08777701 ~~[Attorney Docket No. UPA002 (8261/3~~)], the disclosure of which is incorporated herein by reference.

The fractally designed microchannels readily allow, e.g., the growth of organisms in a culture to be monitored on the basis of flow impedance due to changes in fluid viscosity which can be detected, e.g., optically through a transparent cover over the substrate. The presence and growth of an organism in a sample will influence the flow characteristics within the fractal. One or more pressure sensors may be utilized to detect pressure changes due to changes in fluid properties caused by the presence of an analyte in or beyond the fractal flow paths. Changes in conductivity upon analyte binding also may be readily detected through electrical conductivity sensors in contact with the flow region. For example, clogging of the fractal region 40 of device 10 in Figure 4, which blocks flow of analyte from input port 16A to outlet port 16B may be detected by a conventional conductivity probe 17, whose output is indicative of the presence or absence of aqueous fluid in the outflow channel. Binding moieties may be provided in fractal region, e.g., immobilized on the surface of the fractal flow path, or on a solid phase reactant such as a bead, to bind to the analyte and enhance flow restriction in the fractal flow path.

polymerase cycling reaction is complete, ports 16A and 16C are closed, port 16D is opened, and the reaction products are delivered to detection chamber 22, which contains a labeled polynucleotide probe, e.g., a probe immobilized on a fluorescent bead. Polymerization product is detected by observing the agglutination of the labeled probe and the polymerized polynucleotide product, e.g., visually through a translucent cover disposed over the detection region. Methods and apparatus for mesoscale PCR analyses are described in USSN 07877662 ~~[Attorney Docket No. UPA004 (8261/5)]~~, the disclosure of which is incorporated herein by reference.

In another embodiment, the devices may be utilized to perform an enzyme reaction in which the mixing and addition of sample and reagent components is timed, as is illustrated in the device 10 shown schematically in Figure 21. The substrate 14 of device 10 is microfabricated with inlet ports 16, flow channels 20, the reaction chambers 22A and 22B and the detection chamber 22C. The reaction chambers 22A and 22B each comprise a tortuous mesoscale flow channel. The path length of the tortuous channel can be designed to permit the timed mixing and addition of sample and reagent components. The device may be utilized in combination with an appliance with ports mated to ports in the device, capable of delivering and receiving fluids through the flow system of the device, and optionally, capable of optically detecting a positive result in the detection chamber. In one embodiment, the cholesterol content of a sample may be assayed. Cholesterol esterase is applied via inlet port 16A, and buffer and sample are added via inlet ports 16B and 16C. The mixture then flows through channel 20D to the